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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/785,156	02/25/2004	Lakshman R. Sehgal	3840-006-27	8149

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 06/09/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/785,156	SEHGAL ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-8 and 10-30* is/are pending in the application.

4a) Of the above claim(s) *10-14 and 16-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,15 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 10-14 and 16-29 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/12/06. A complete reply to this final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Objections

Claim 1 is objected to because of the following informalities: Claim 1 recites "a stuffer sequence comprises a HPRT intron sequence". This phrase is grammatically incorrect, and "comprises" should be replaced with --comprising-- or --that comprises--. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 1, 2, 5-8, 15, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to limit the claimed method to treating an atherosclerotic cardiovascular disease and to recite "administering to said mammal at a site susceptible to a thrombus." New claim 30 also recites this limitation. Claim 15, directed to different routes of administration, has not been amended in conjunction with claim 1, and is directed in part to subcutaneous or intramuscular administration to the thrombus site. Applicant does not indicate where these limitations are supported by the original specification, or how, as is Applicant's burden. See MPEP 714.02, last sentence of the third paragraph from the end and 2163.06 (I) last sentence. The specification does not explicitly or implicitly suggest administering the adenovirus to a generic "site susceptible a thrombus," which may include any tissue into which blood has leaked, in the treatment of an atherosclerotic cardiovascular disease, as alleged. The original specification at page 32 describes the administration of the adenovirus in treatment of an atherosclerotic cardiovascular disease, and teaches that it is administered to a vascular site of thrombus. There is no teaching here to administer the vector to a thrombus site that is not a vascular site, and there is no teaching to administer the vector in this context "subcutaneously, or intramuscularly" as recited in claim 15. Consequently, there is no evidence that Applicant had contemplated or possessed the broader method now being claimed, and the claims therefore include impermissible new matter.

Claim 1 has also been amended to recite "gutless adenovirus comprises ... a stuffer sequence comprises a HPRT intron sequence" (*sic*). Applicant indicates that the latter limitation is supported in the original specification at page 13, lines 7-9, and Figure 1. Page 13, lines 7-9, of

the specification as filed does not describe this feature, it is assumed that Applicant means page 12, line 25, to page 13, line 2.

However, page 12, line 25, to page 13, line 2, does not describe a generic stuffer sequence that comprises "a HPRT intron sequence". Rather it specifically refers to the species of stuffer sequence shown in Fig. 1, which consists of, in order relative, HPRT introns 5, 4 and 3. The claims as written embrace any embodiment where the stuffer includes any HPRT intron as well as any other sequence. There is no evidence from the original disclosure that Applicant had contemplated or possessed the broader "stuffer sequence" now recited in the claims, and the claims therefore include impermissible new matter.

Claims 5 and 30 recite the limitations that the adenovirus vector comprise a sequence encoding SEQ ID NO: 2 operably linked to a regulatory element and the nucleotide sequence of SEQ ID NO: 4, which is the nucleotide sequence of an expression cassette comprising a CMV promoter and coding sequence for SEQ ID NO: 2 (see Example 2). Consequently, claims 5 and 30 require there to be two separate expression cassettes for expression of TM. Applicant does not indicate where these limitations are supported by the original specification, or how, as is Applicant's burden. Example 2 describes the construction of a species of adenovirus vector readable on the vector recited in claim 1, wherein the regulatory element and TM coding sequence are SEQ ID NO: 4. There appears to be no support in the original disclosure for an adenovirus vector comprising two expression cassettes for expression of TM. Thus, there is no evidence from the original disclosure that Applicant had contemplated or possessed this type of adenovirus vector now recited in claims 5 and 30, and these claims therefore include impermissible new matter.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "the promoter" in line 2. There is insufficient antecedent basis for this limitation in the claim. Claim 1 recites "regulatory element", not promoter.

Claim Rejections - 35 USC § 103

Claims 1, 2, 6-9 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Bach et al., WO 96/06933, as applied to claims 1-3, 6-9, and 15 above or Waugh et al. (Circulation 102(3): 332-337, July 2000) as applied to claims 1-3, 6, 9, and 15 above, and further in view of Vassalli et al. (Cardiovasc. Res. 35: 459-469, 1999); Umana et al. (Nat. Biotech. 19(6): 582-585, Jun. 2001); and Parks et al. (J. Virol. 73(10): 8027-8034, Oct. 1999) as evidenced by GenBank Acc. No. M26434.

Bach et al. discloses a method for treating thrombosis, including that associated with systemic or local inflammatory conditions including atherosclerosis, in a mammal by administering an expression vector to the affected tissue, primarily endothelial tissue (vascular tissue) that encodes thrombomodulin, wherein the thrombomodulin coding sequence is operably linked to a constitutive, tissue-specific or regulatable promoter (pages 3-4, 9, 13, 14, claims 2-10). More specifically, adenoviral vectors can be used (pages 6, 11-13), and the thrombomodulin is human thrombomodulin (page 15). Bach does not teach a gutless adenoviral vector with a stuffer sequence comprising an HPRT intron.

However, Vassalli teaches that while adenoviral vectors are the vector of choice for vascular gene therapy, their use is limited by short transgene expression due to T-cell mediated response to transfected cells in response to expression of viral proteins. Vassalli (page 460) suggests that adenoviral vectors lacking all viral genes, i.e. gutless adenoviral vectors, may minimize or eliminate this problem, and that early results showed this result.

Parks discloses that effective packaging and stability of gutless adenoviral vectors requires the vectors to be within 75%-100% of the wild-type adenoviral genome. The size constraints are met by the inclusion of stuffer DNA in the vector (page 8028, col. 1). Parks describes 20-22 kb stuffer DNAs from two different sources - one derived from phage lambda genomic DNA and the other from the human HPRT gene. Parks disclosed that expression of the transgene from the gutless vector was higher if the stuffer DNA was from the HPRT gene than from phage lambda DNA. Parks does not disclose the exact identity of the HPRT DNA used (Abstract, page 8028, Fig. 1). However, as shown in GenBank Acc. No. M26434, it is not possible to obtain a 20-22 kb fragment of the HPRT gene without including one or more introns (see sheet 4, "CDS" under features). Consequently, the 22 kb fragment disclosed in Parks necessarily included an HPRT intron. Parks also discloses that gutless adenoviral vectors provide long-term high-level gene expression *in vivo* (page 8028, col. 1).

Umana, published years after Vassalli, details how to make sufficient quantities of gutless adenoviral vectors, and reiterates that gutless vectors mediate long term expression (see abstract).

Therefore, it would have been obvious to one of skill in the art to have utilized a gutless adenovirus in place of older adenoviral vectors in the method of Bach to take advantage of the longer expression times afforded by gutless adenoviral vectors compared to the older adenoviral

vectors as taught in Vassalli, Parks and Umana. Parks taught the necessity of making a gutless vector of a size between 70% to 100% of the wild-type adenoviral genome using stuffer DNA, and that a stuffer comprising an HPRT intron was superior to a stuffer DNA from phage lambda. Umana shows that at the time the instant invention was made, one of skill in the art was aware of methods for producing sufficient quantities of gutless adenoviral vectors for use in gene therapy.

Claims 1-2, 6, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waugh et al. (Circulation 102(3): 332-337, July 2000) in view of Vassalli et al. (Cardiovasc. Res. 35: 459-469, 1999); Umana et al. (Nat. Biotech. 19(6): 582-585, Jun. 2001); and Parks et al. (J. Virol. 73(10): 8027-8034, Oct. 1999) as evidenced by GenBank Acc. No. M26434.

Waugh discloses a method for treating restenosis by administering an adenoviral vector encoding human thrombomodulin under control of a constitutive RSV promoter to the location of an artery where restenosis, which includes thrombosis, may occur in treating atherosclerotic disease by balloon angioplasty (see entire reference, especially, abstract for overview, and page 333, col. 1). Waugh does not teach a gutless adenoviral vector with a stuffer sequence comprising an HPRT intron.

However, Vassalli teaches that while adenoviral vectors are the vector of choice for vascular gene therapy, their use is limited by short transgene expression due to T-cell mediated response to transfected cells in response to expression of viral proteins. Vassalli (page 460) suggests that adenoviral vectors lacking all viral genes, i.e. gutless adenoviral vectors, may minimize or eliminate this problem, and that early results showed this result.

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Therefore, it would have been obvious to one of skill in the art to have utilized a gutless adenovirus in place of older adenoviral vectors in the method of Waugh to take advantage of the longer expression times afforded by gutless adenoviral vectors compared to the older adenoviral vectors as taught in Vassalli, Parks and Umana. Parks taught the necessity of making a gutless vector of a size between 70% to 100% of the wild-type adenoviral genome using stuffer DNA, and that a stuffer comprising an HPRT intron was superior to a stuffer DNA from phage lambda. Umana shows that at the time the instant invention was made, one of skill in the art was aware of methods for producing sufficient quantities of gutless adenoviral vectors for use in gene therapy.

Applicant's arguments filed 5/13/06 have been fully considered to the extent they apply to the new rejections set forth above, but they are not persuasive. Applicant points out that none of Bach, Waugh, Vassalli and Umana disclose all of the limitations of the claims, and that gene therapy in general is an unpredictable art, and concludes from this that the rejection was based upon an improper "obvious to try" rationale. In response, had any one of the cited references disclosed all the limitations of the claims, the rejection would have been improper for not being made under 35 USC 102, rather than 35 USC 103. Applicant's point here is unclear. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Also, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The grounds of rejection indicated what the prior art taught and why one of ordinary skill in this art would have been motivated to arrive at the claimed invention based upon the prior art disclosures. Finally, Applicant is reminded that the enablement requirement is a requirement of the specification to enable the claimed invention. Simply because the instant application did not fully enable the original claims, is not evidence that prior art disclosures are not enabling. Applicant has the burden of showing that the prior art is not enabled (see MPEP 2121 and 2121.01), and has not done so.

Applicant also asserts that gutless adenoviral vectors are difficult to construct and produce in large quantities, and goes on to make several additional unsupported assertions regarding the difficulties involved in producing gutless adenoviral vectors. In response, Applicant has not explained how the cited prior art is deficient in this regard. Enablement, or the lack thereof, is not dependent the amount or difficulty of experimentation required, but whether such experimentation is undue. It is not relevant to the rejections that producing gutless adenoviral vectors is difficult, since the evidence of record shows that one of ordinary skill in this art knew how to make such vectors and prepare sufficient quantities of them for use in gene therapy. The instant specification tacitly acknowledges that the preparation of these vectors was well within the skill of practitioners of this art, since the specification relies on the prior art for the methods of making and preparing such vectors in general; see specification at pages 12 and 36-39, which direct one to prior art on the construction and production of gutless vectors, including Umana (spec. page 37) which is cited in the rejections.

Applicant refers to Kagawa et al. in the arguments. However this document has not been made of record. Consequently, the arguments pertaining to it have not been considered.

Conclusion

Claims 5 and 30 are free of the prior art of record, none of which suggests a gutless adenoviral vector comprising SEQ ID NO: 4, much less one also comprising a second TM expression cassette. Limiting the stuffer sequence in claim 1 to the stuffer shown in Fig. 1 would overcome the rejections under 35 USC 103, and partly overcome the rejection for new matter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Scott D. Priebe

Scott D. Priebe, Ph.D.
Primary Examiner
Art Unit 1633